Author's response to reviews

Title: Safety and Efficacy of Anti-PCSK9 Antibodies: A Meta-analysis of 25 Randomized, Controlled Trials

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Author's response to reviews: see over
Dear Dr. Ursula D'Souza, Yoon Kong Loke, and Evangelos N. Liberopoulos,


We thank the editor and both reviewers for their time and effort devoted to evaluate our manuscript. Their suggestions and comments have made the data of this revision better to read and the manuscript greatly improved. We have made point-by-point responses to all the queries raised by reviewers in this cover letter. Particularly in the statistical section and discussion section, we made numerous revisions to obtain a better scientificity and readability. We corrected all the mistakes which were not fully demonstrated in the previous submission. Revisions have been made by using “track changes” in MS Word program or have been red-marked. The revised manuscript was renamed as “Revised Manuscript with Track Changes”. The reviewers’ and editor’s original critiques are cited in bold and italic, followed by our responses.

To Dr. Yoon Kong Loke:

Minor essential revisions:

Quality assessment - it is not clear to me how you detected selective reporting of adverse events. Also, did you collect information on what the trialists said they were going to do in monitoring adverse events?

We agree with Dr. Yoon Kong Loke that selective reporting of adverse events might exist and could bring bias into analysis of several safety endpoints. We have added this statement in our limitation section. Notably, no obvious selective reporting bias was detected in major safety endpoints, such as any TEAE, serious TEAE, abnormal liver function, abnormal kidney function, injection-site reactions and musculoskeletal disorders etc. To minimize this
bias, we reviewed all the materials (including supplementary materials and relevant publications in other papers) provided by all these studies and extracted and analyzed all these data. In addition, we collected the safety endpoints and the methods of monitoring safety outcomes in these trials (Table S2 in Additional file 2). Selective reporting bias was mainly attributable to conference presentations included in our meta-analysis, which did not report minor safety outcomes such as gastrointestinal disorders.

**Statistical analysis - you should state that continuity correction was added to zero cells? What was the correction, and was it added to both cells?**

We thank Dr. Yoon Kong Loke for making this valid comment and suggestion. Trials in which the event of interest was not detected in any of the treatment groups were excluded in the analysis of that endpoint. For studies in which only one of the groups had no event of interest, the estimate of treatment effect and its confidence interval were calculated after adding 0.5 to each cell of the 2 × 2 contingency table for the trial. We added this statement in the revised statistical analysis section, and two references of this statistical method at the same time.

**Results, study selection and characteristics - should state the duration of most of the RCTs - majority seem to be less than 12 weeks, and there are very few long-term trials?**

We thank Dr. Yoon Kong Loke for pointing this out. We have added the length of follow-up in the “study characteristics” part in the results section. Regarding evolocumab, all trials were followed up for 12 weeks, except the OSLER and DESCARTES trials, which were followed up for 52 weeks. With regard to alirocumab, most trials were followed up for 24 weeks except 3 phase 2 trials which were followed-up for 8 to 12 weeks.
Discussion - there is too much emphasis on absence of statistically significant safety issues. You should point out major Limitations in safety data:

- Broad 95% CI in some estimates, making it impossible to rule in or rule out problems
- Lumping of broad categories into TEAE, SAE, so no ability to detect increased risk of specific events
- Small, short-term trials cannot detect serious, rare problems

We thank Dr. Yoon Kong Loke for making this valuable comments and suggestions. In the revised discussion section, we pointed out all these limitations from the fourth to the fifth limitation in our manuscript. We also added some contents raised by reviewer Dr. Evangelos N. Liberopoulos to improve the readability our discussion section.

You make a statement at the end about 0.5 correction added to zero cells. Your statement is incorrect. The 0.5 added is purely for calculation purposes of RR/OR in the meta-analysis. It should not be used to affect the raw numbers (totals of events/patients. Also, the continuity correction does not necessarily lead to over-estimate, it could work in either direction depending where the continuity was. Usually, it biases towards the null.

Statistical review: Yes, and I have assessed the statistics in my report.

We agree with Dr. Yoon Kong Loke that the continuity correction does not necessarily lead to over-estimate of the incidence of safety outcomes, and we have removed the wrong statement in our revised manuscript.

To Dr. Evangelos N. Liberopoulos:
This is an excellent and very informative meta-analysis on a very hot topic.

Some minor comments:
- All abbreviations should be defined when first used in the text (e.g. LDL-C).
- Page 7; line 15: one study was not.
- Page 7; line 16: too few.
- Page 13; lines 15-16: needs rephrasing.

We thank Dr. Evangelos N. Liberopoulos for making these valuable corrections, and we are pleased to learn that Dr. Evangelos N. Liberopoulos considered our manuscript “informative”. We have corrected all these ill-formed mistakes and defined every abbreviation in the text at first use.

The very recent New England Journal of Medicine publications regarding the effect of antiPCSK9 antibodies on CVD events (ODYSSEY LONG TERM and OSLER trials) should be included and discussed.

We thank Dr. Evangelos N. Liberopoulos for pointing out these two very recently published trials regarding the two anti-PCSK9 antibodies analyzed in our study. The ODYSSEY LONG TERM and OSLER trials have been included in our meta-analysis in our initial submission, although a bit different from their appearance in NJEM. At first, the ODYSSEY LONG TERM trial was presented at 2014 Scientific Sessions of European Society of Cardiology on August 31, 2014 in Barcelona (included in our meta-analysis), the results presented at this conference was extremely similar as it was recently published in NEJM (doi:10.1056/NEJMoa1501031), therefore, we only added the contents of this newly published paper in our discussion section, especially regarding CVD events. Meanwhile, the newly published OSLER trial (doi:10.1056/NEJMoa1500858) was an extension study of two trials—OSLER-1 and OSLER-2: the follow-up was extended to about 1 year.
The parent trial of OSLER-1 trial was named as “OSLER” trial (Circulation, 2014, 129: 234-243) and was included in our prior manuscript. The main difference between “OSLER” trial (Circulation, 2104, 52-week follow-up) and the OSLER-1 trial (NJEM, 2015, 56-week follow-up) was that the OSLER-1 trial also included the YUKAWA trial, which was carried out in Japan but was also separately included in our previous manuscript. The OSLER-2 trial was an extension study of several phase 3 studies of evolocumab, i.e. MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DESCARTES and THOMAS-1/2 trials. Of note, most of these parent trials (MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DESCARTES) were included in our prior submission, except the THOMAS-1/2 trials which was not published separately, but the number of patients enrolled in THOMAS-1/2 trials was small (222 patients in total, including treatment group and control group). Therefore, we kept encompassing all these parent trials as individual trials in our meta-analysis instead of replacing them with the single united trial, but indeed, we discussed these two united trials in our revised submission.

Quality of written English needs some language corrections before being published.

Thanks. We made our great efforts to edit the English of our manuscript. We hope the readability of our manuscript would not hinder the understanding of the scientific contents.

We thank Dr. Ursula D'Souza, Yoon Kong Loke, and Evangelos N. Liberopoulos for all these careful and valuable comments and hope to have properly addressed all the queries.

Yours sincerely,
On behalf of my coauthors,
Biao Xu M.D., Ph.D.